Examiner Jennifer Kim 703-746-5156

Attorney Docket No.: 5739.200-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weibel et al.

Application No.: 09/450,609 Group Art Unit: 1617

Filed: November 30, 1999 Examiner: Kim, J.

For: New Pharmaceutical Composition And The Process For Its Preparation

Confirmation No.: 7926

CERTIFICATE OF FACSIMILE TRANSMISSION

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby certify that the attached correspondence comprising:

- Amendment Fee Transmittal and Petition to Extend TIme Amendment

is being transmitted via telefax to Examiner Jennifer Kim at (703) 308-4556.

Respectfully submitted,

Date: 7/24/03

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Attorney Docket No.: 5739.200-US

PATENT

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AMENDMENT FEE TRANSMITTAL

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P.O. Box 1450
Alexandria, VA 22313

Sir:

It is respectfully requested that the time for response to the Office Action dated March 25, 2003 be extended for a period of one month from July 25, 2003 to August 25, 2003. Applicant hereby petitions for such extension of time.

No additional claims fees are required.

Please charge the required fee, estimated to be $110, and any other additional fees that may be required to Novo Nordisk Pharmaceuticals, Inc., Deposit Account No. 14-1447. A duplicate of this sheet is enclosed.

Respectfully submitted,

Date: 7/24/03

Cheryl H. Agris

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AMENDMENT AND REMARKS UNDER 37 C.F.R. 1.116

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Sir:

In response to the final Office Action issued March 25, 2003, please consider the following amendments and remarks.

CLAIM AMENDMENTS

Claims 1-5 have been cancelled.

6. (Previously amended) A pharmaceutical composition comprising 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients with low water content comprising anhydrous lactose, microcrystalline cellulose, magnesium stearate, and talc.

7. (original) The pharmaceutical composition according to claim 6 in the form of a tablet, a powder or a capsule.

Claim 8 is cancelled.

9. (Currently Amended) ~~The pharmaceutical composition according to claim 6 wherein the pharmaceutically acceptable excipients are~~ A pharmaceutical composition comprising 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, between 100 and 400,000 parts by weight of anhydrous lactose, between 1000 and 10,000 parts by weight of microcrystalline cellulose, and between 10 and 500 parts by weight of magnesium stearate, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts.

Claims 10-11 are cancelled.

12. (original) The pharmaceutical composition according to claim 6, wherein the pharmaceutically acceptable excipients have a very low water content.

Claim 13. (original) The pharmaceutical composition according to claim 6, wherein the pharmaceutically acceptable excipients are in a dry form.

Claims 14-15 are cancelled.

16. (previously amended) The pharmaceutical composition according to claim 6, further comprising at least one sweetener, flavouring agent, colour or lubricant.

Claims 17-27 are cancelled.

28. (previously added) The pharmaceutical composition according to claim 6 in tablet form, wherein the tablet is formed by direct compression.

29. (previously amended) The pharmaceutical composition according to claim 6 consisting of

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl] thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof	9%
Microcrystalline cellulose	20%
Anhydrous lactose	66%
Magnesium Stearate	0.5%
Talc	4.5%

30. (previously added) The pharmaceutical composition according to claim 29 in the form of a tablet, a powder or a capsule.

31. (previously added)The pharmaceutical composition according to claim 30 in tablet form, wherein the tablet is formed by direct compression.

REMARKS

Claims 6, 7, 11-13, 16 and 28-31 are pending in the above-referenced application. Claim 9 has been amended so that it is now in independent form.

1. The Rejection Under 35 U.S.C. 103(a)

Claims 6, 7, 9, 11-13, 16, and 28 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over Lohray et al. (WO9741097) in view of Sohda et al. (U.S. Patent No. 5972971). The Office Action specifically states:

> Lohray et al. at page 34, lines 27-29, page 35, example, and page 7, lines 13-14, teach pharmaceutical composition containing applicants' active agent in tablet, capsule, or powder form, in combination with the pharmaceutically acceptable excipient set forth in claim 8-10, and flavourants, sweeteners set forth in claim 16, and other media normally not employed in preparing such compositions.
>
> Sodha et al. at abstract and column 10, lines 20-21, teach anti-diabetic agent containing anti-oxidants, preferably ascorbic acid. Sohda et al. also teach at column 9, lines 55-65, the anti-diabetic agent containing applicants' excipient such as lactose, mannitol, starch, crystalline cellulose, silicone dioxide, magnesium stearate, and hydroxy propyl methyl cellulose.
>
> The difference between the primary reference and applicants' claimed invention is the presence of anti-oxidant set forth in claims 6,14, and 15, and the proportions set forth in claims 8 and 9. However, to incorporate anti-oxidant to the primary reference would have been obvious to a person of ordinary skill in view of Sohda et al. who teach antidiabetic agent containing anti-oxidant and other excipient. One in ordinary skill in the art would have been motivated to combine anti-oxidants to the above composition since Lohray et al. teach other media normally employed can be incorporated and anti-oxidant is normally incorporated by Sohda et al. in formulating anti-diabetic agent.

With respect to the Declaration filed with the previous response, the Office Action states:

Applicants argue that data shows nonobvious and unexpected result of the formulations containing microcrystalline cellulose with low moisture content (Avicel PH 112, formulation B and D) are more stable, i.e., lower content of degradation products than the formulations containing microcrystalline cellulose with higher moisture content (Avicel PH 102, formulation A and C). However, this is not persuasive because Applicants' broad claims 6 and 9 read on both sets of formulations (B and D) and (A and C). The "evidence" of alleged nonobvious and unexpected result is not commensurate in scope with the breadth of the claims. It is noted that Applicant's alleged nonobvious and unexpected results is only encompassed by the specific formulation of B and D not the claims drawn to broad class of a microcrystalline cellulose.

Applicants respectfully traverse the rejection. First, Applicants note that claim 6 in its present form does not contain any reference to an anti-oxidant. Specifically, in the composition as claimed, an anti-oxidant is not an essential ingredient. Second, there is absolutely no suggestion or discussion in Lohray regarding the desirability of low water content in excipients. Applicants note that on page 35, in production example a), the ingredients active ingredient, lactose and corn starch are uniformly blended with water and granulated after drying under reduced pressure; carboxymethyl cellulose and magnesium stearate are subsequently added. In production example b), the active ingredient, calcium phosphate, lactose and corn starch were moistened with an aqueous solution of polyvinyl pyrrolidone and granulated after drying under reduced pressure. Magnesium stearate was added and granules were compressed. Clearly, given the teaching of Lohray, it would have not been obvious to consider using anhydrous lactose and/or cellulose with low water content.

Applicants further note that Lohray in Example 28 on page 80 merely teaches the method used to obtain the active compound, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione. This method certainly does not use anhydrous conditions to obtain said active compound.

Applicants would like to further clarify the significance of the results set forth in the Declaration filed with the response filed on August 23, 2002. First, as previously discussed, formulations B and D containing Avicel PH 112, were more stable than formulations A and C, containing Avicel PH 102. Avicel PH 112 has a lower moisture content than Avicel PH 102. Second, formulations C and D containing anhydrous lactose were more stable than formulations A and B which did not contain anhydrous lactose. The results set forth in the declaration are indeed unexpected in view of the teachings of Lohray and support Applicants assertions that a formulation of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione containing excipients with low water content comprising anhydrous lactose, microcrystalline cellulose, magnesium stearate, and talc (claim 6) and a formulation of comprising 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
between 100 and 400,000 parts by weight of anhydrous lactose,
between 1000 and 10,000 parts by weight of microcrystalline cellulose, and
between 10 and 500 parts by weight of magnesium stearate,

expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione

would not be obvious over the teachings of Lohray. There is certainly no indication in Lohray that using anhydrous cellulose would increase the stability of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione. Actually, in the production examples of Lohray, the active ingredient and lactose are moistened.

Applicants assert that the Sohda reference would not add anything further to the disclosure of Lohray. There is certainly no suggestion or disclosure in the Sohda et al. reference regarding the use of low moisture formulations. Furthermore, Applicants assert that one of ordinary skill in the art would not be motivated to combine Lohray et al. with Sohda et al. This is because Sohda et al. is directed to a completely different class of compounds, 2,4-oxazolidinedione compounds.

In view of the above arguments, Applicants assert that the rejection s under 35 U.S.C. 103(a) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone at (914) 712-0093 if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: 7/24/03

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● **Comments:**

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